

### **Remarks/Arugments**

Claims 1-13, 16-28 and 59-63 are pending in this Application. Claims 61-63 are allowed. In the Office Action mailed November 2, 2005, Claims 1-13, 16-20, 24-28, and 59-60 are rejected for the reasons presented below:

1. Claims 20, 24-28 are rejected under the judicially created doctrine of obviousness-type double patenting; and
2. Claims 1-13, 16-19, 59-60 are rejected under 35 U.S.C. § 112, second paragraph.

Applicants respectfully address the basis for each of the Examiner's rejections below.

#### ***Claims Rejection – Obviousness-type Double Patenting***

On page two of the Office Action, the Examiner rejected Claims 20, 24-28 under the judicially created doctrine of obviousness-type double patenting as being unpatentable over Claim 12 of US Patent No. 6,329,208. Applicants respectfully enclose with this reply a Terminal Disclaimer to Obviate a Double Patenting Rejection Over a "Prior" Patent in which the Applicant obviates the obviousness-type double patenting rejection over the "prior" patent stated to be U.S. Patent No. 6,329,208. Entry and allowance of the enclosed Terminal Disclaimer is respectfully requested. The Terminal Disclaimer is signed by an authorized attorney or agent of record acting as a representative under 37 C.F.R. § 1.34 for actions taken by the Assignee under 37 C.F.R. § 3.71 and § 3.73(b). Establishment of the Assignee as owner of this Application for patent is provided in the submission of documentary evidence of a chain of title from the original owner to the Assignee that has been recorded in the Assignment Records Office of the United States Patent and Trademark Office (USPTO) on August 29, 2001, under Reel 012116 and Frame 0917, a copy of which is attached hereto. A submission establishing ownership is also provided in the form of a copy of the Election under 37 C.F.R. §§ 3.71 and 3.73 and Power of Attorney document signed by a person having

apparent authority to sign on behalf of the Assignee as an officer of the Assignee, which was filed with the Assignment Records Office of the USPTO on August 27, 2001. These submissions are being provided at the same time as this paper requesting and taking action on behalf of the Assignee. An Associate Power of Attorney document signed by an authorized attorney or agent of record acting as a representative of the Assignee (in accordance with 37 C.F.R. § 1.34 and the Election under 37 C.F.R. §§ 3.71 and 3.73 and Power of Attorney document provided herein) is provided with this Amendment to appoint the attorney or agent signing the Terminal Disclaimer and this Amendment full power to prosecute this Application for patent, to make alterations and amendments thereto and to transact all business connected herewith with the United States Patent and Trademark Office. Accordingly, the Terminal Disclaimer and this Amendment are heretofore signed by an attorney or agent of record acting in a representative capacity as provided by 37 C.F.R. § 1.34.

With this Amendment, Applicants respectfully submit amended Claims 20 and 25, amended as to matters of form and to further define the subject matter of the invention as described in the claim. No new matter is introduced with amended Claims 20 or 25. Support for amended Claims 20 and 25 are found in the Specification. For amended Claim 20, see, for example, paragraph [0013] and Claim 54 of the originally filed Application for patent. Applicants submit that the content of the original claim may be relied on because the claim, itself, constitutes a clear disclosure of this subject matter. Accordingly, Applicants respectfully request entry and allowance of amended Claims 20 and 25.

***Claims Rejection – 35 U.S.C. § 112, second paragraph***

On page three of the Office Action, the Examiner rejected Claims 1-13, 16-19, 59-60 under 35 U.S.C. § 112, second paragraph, for the reasons set forth below.

Claim 7 is rejected for having insufficient antecedent basis. Applicants respectfully submit amended Claim 7, amended to provide proper antecedent basis to Claim 4. Applicants respectfully request the entry and allowance of amended Claim 7.

Claims 1-13, 16-19, 59 and 60 are rejected as being incomplete for omitting a step of how the relative NMR measurement is made. Applicants respectfully submit amended independent Claims 1, 16, 17, 19 and 59, amended to include how the relative NMR measurement is made. The claims are amended to state that gluconeogenesis is measured “by comparison of relative nuclear magnetic resonance signal areas in a spectrum obtained from” labeled components in the analyte. [Emphasis added to show amended text.] Support for these amendments is found in the Specification, see e.g., paragraphs [0013], [0029], [0030], [0031], [0035], [0037], [0040], [0044], [0050], portions of which are provided in the paragraphs identified below.

[0029] . . .  $^1\text{H}$  NMR spectra were obtained with the same spectrometer using a 5 mm indirect probe. Spectra were acquired with a  $90^\circ$  pulse following pre-saturation of the residual water signal and a 15 s interpulse delay. . . . All NMR spectra were analyzed using the curve-fitting routine supplied with the NUTS PC-based NMR spectral analysis program (Acorn NMR Inc., Fremont CA).

[0037] Figure 4 shows a  $^2\text{H}$  NMR spectrum of monoacetone glucose derived from 2 pooled plasma extracts (corresponding to 20 mL of whole blood). The area of each resonance is proportional to  $^2\text{H}$ -enrichment at that position, so the spectrum provides a simple and direct readout of  $^2\text{H}$  enrichment ratios.

[0050] . . . Most importantly, the  $^2\text{H}$  NMR spectrum of monoacetone glucose shows separate resonances for the prochiral H6 hydrogens of glucose while exchange of  $^2\text{H}_2\text{O}$  at the level of fumarase in the TCA cycle specifically enriches the H6S position.

Applicants further submit that, contrary to the Examiner’s statement in paragraph 5 of page 3, an essential step of Claims 1-13, 16-19, 59 and 60 is not that “a comparison is made between the NMR of the labeled components and a calibration curve of the normal NMR of the components.” Applicants submit that the Specification merely

indicates that a calibration step, similar to that described above, may be used but does not disclose or suggest that it is essential. In fact, the Specification describes in paragraph [0029] that calibration is not essential by stating, "A comparison of  $^2\text{H}$  signal areas in spectra collected using these standard pulsing conditions with those measured in spectra collected using a 1.0 s acquisition time (sufficient for complete relaxation) were identical to within 7%." The Specification further submits that some corrections may be applied if desired at certain acquisition times by stating, "Nevertheless, small correction factors were used to allow for partial saturation when using the 0.512 s acquisition conditions." The above statements do not state that such corrections are essential. Accordingly, Applicants respectfully submit that the comparison identified by the Examiner in paragraph 5 of page 3 is not necessary in the instant claims. Applicants respectfully request acceptance and allowance of amended Claims 1, 16, 17, 19 and 59 (amended as described above) and claims depending therefrom. Claims 14 and 15 have been canceled. In addition, Claims 1, 3, 11, 16, 17, 19 and 59 have been amended as to matters of form; their entry and acceptance are respectfully requested.

Claims 5 is rejected for being indefinite. Applicants respectfully submit amended Claim 5, amended to particularly point out and distinctly claim the subject matter regarded as the invention. Claim 5 has been amended to describe the analyte as "glucose deuterated in the 2, 5 and 6S position, and any transformation in glucose that maintains the 2,5 and 6 positions in relation to one another." [Emphasis added to show amended text.] Support for amended Claim 5 can be found in the Specification (see e.g., paragraph [0031]) and Claims 5 and 16 of the originally filed Application for patent. Applicants submit that the content of the original claims may be relied on because the claims, themselves, constitute a clear disclosure of this subject matter. Applicants further submit that in accordance with the Specification (see e.g., paragraph [0031]) and contrary to the Examiner's statement in paragraph 6 of page 3, claim 5 as amended is correct in stating that the analyte (and not the "deuterium source") is glucose deuterated in the 2, 5 and 6S positions. Applicants respectfully request entry and allowance of amended Claim 5.

Claims 12 and 26 are rejected for being indefinite. Applicants respectfully submit amended Claim 12 and 26, amended to particularly point out and distinctly claim the subject matter regarded as the invention. Claims 12 and 26 have been amended to describe the Krebs cycle precursor as “pyruvic acid, acetic acid, acetoacetic acid, and beta-hydroxybutyric acid.” [Emphasis added to show amended text.] Support for amended Claims 12 and 26 can be found in the Specification, see e.g., paragraph [0003] and FIGURE 1. Applicants respectfully request the entry and allowance of amended Claims 12 and 26.

With this Amendment, Applicants also respectfully submit amended Claim 61, amended as to matters of form and to provide proper antecedent basis. No new matter is introduced with amended Claim 61. Entry and allowance of amended Claim 61 is respectfully requested.

### Conclusion

In light of the amendments, remarks and arguments presented above, Applicants respectfully submit that claims as provided in the Listing of Claims beginning on page 5 of this paper are in condition for allowance.

A Terminal Disclaimer to Obviate a Double Patenting Rejection Over a "Prior" Patent is also transmitted with this Amendment along with submissions including a copy of a fully executed Assignment, an Election under 37 C.F.R. §§ 3.71 and 3.73 and Power of Attorney, and an Associate Power of Attorney document. It is believed that no additional fees are due with this Amendment. If this is incorrect, the Commissioner is authorized to charge the additional fees, other than the issue fee, that may be required by this paper to Deposit Account No. 07-0153.

If the Examiner has any questions or comments, or if further clarification is required, it is requested that the Examiner contact the undersigned at the telephone number listed below.

Dated: February 2, 2006

Respectfully submitted,

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